CLAIMS

What is claimed is:

1. A construct comprising a metal ion-binding domain comprising two or more linked residues forming an N_3S_1 ligand available for complexing with a metal ion, wherein the construct is conformationally constrained in a structure specific for one or more melanocortin receptors upon complexing the metal ion-binding domain with a metal ion.

2. A manufactured peptide and pharmaceutically acceptable salts thereof comprising a metal ion-binding domain comprising two or more contiguous amino acids and a determined biological-function domain specific for one or more melanocortin receptors, wherein at least a portion of said biological-function domain is co-extensive with at least a portion of the metal ion-binding domain, and wherein said biological-function domain is conformationally constrained upon complexing the metal ion-binding domain with a metal ion.

3. A combinatorial library targeted to melanocortin receptors of different sequence peptide members synthesized on solid phase, where each constituent library member comprises:

(a) a peptide sequence of three or more amino acid residues bound to solid phase characterized by (i) a sequence of two or more amino acid residues forming a metal ion-binding domain and including at least one amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group, (ii) a sequence of one or more amino acid residues at the N- or C- terminus of the metal ion-binding domain, or at both the N- and C-terminus of the metal ion-binding domain, and (iii) a cleavable bond attaching the peptide sequence to solid phase; and

(b) a unique selection or sequence of amino acid residues in the peptide sequence of at least one of the constituent members of the library;

wherein the orthogonal S-protecting group may be removed without cleaving the peptide sequence from the solid phase.

4. A combinatorial library targeted to melanocortin receptors of different sequence peptidomimetic members synthesized on solid phase, where each constituent library member comprises:

(a) a peptidomimetic sequence of a combination of three or more amino acid residues and mimics of amino acid residues bound to solid phase characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof forming a metal ion-binding domain and including at least one amino acid residue or mimic of an amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group, (ii) a sequence of on or mor amino acid residues, mimics of amino acid residu s or combinations thereof at the N- or C- terminus of the m tal ion-binding domain, or at both the N- and C-terminus of the m tal ion-binding domain, and (iii) a cleavable bond attaching the p ptidomim tic sequence to solid phase; and

(b) a uniqu selection or sequence of amino acid residues, mimics f amino acid residues or combinations thereof in the peptidomimetic sequence of at least one of the constituent members of the library;

wherein the orthogonal S-protecting group may be removed without cleaving the peptidomimetic sequence from the solid phase.

5. A combinatorial library targeted to melanocortin receptors of different sequence peptid or peptidomimetic members synthesized in solution, where each constituent library member comprises:

(a) a peptidomimetic sequence of a combination of three or more amino acid residues and mimics of amino acid residues bound to solid phase characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof forming a metal ion-binding domain and including at least one amino acid residue or mimic of an amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group, (ii) a sequence of one or more amino acid residues, mimics of amino acid residues or combinations thereof at the N- or C- terminus of the metal ion-binding domain, or at both the N- and C-terminus of the metal ion-binding domain; and

(b) a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof in the peptidomimetic sequence of at least one of the constituent members of the library.

6. The composition of claims 1 or 2 of the formulas:

R_1 – Lll – Aaa – Bbb – Ccc – R_2,

R_1 – Bbb – Aaa – Ccc – R_2,

R_1 – Ddd – Bbb – Aaa – R_3,

R_4 – Eee – Bbb – Ccc – R_2,

R_1 – Fff – Aaa – Ggg – Ccc – R_5,

R_1 – Hhh – Aaa – Bbb – Ccc – R_5, or

R_1 – Iii – Iii – Ccc – Jjj – Kkk – R_2,

wherein

R_1 is any functionality that potentiates the intrinsic activity of the remainder of the molecule, including but not limited to providing an auxiliary or secondary receptor contact. Any of a variety of amino acids and non-peptide groups may be employ d, including an amino acid chain from one to about four neutral or charg d L- or D-configuration amino acid residues. If R_1 is a non-peptid group, it may be a linear or branched alkyl, aryl, alk ne, alk nyl or aralkyl chain;

Aaa is an L- or D-configuration cationic amino acid with a positively charged side chain. Preferred amino acids include L-configuration Lys, Arg, Orn, Dpr or Dbu, and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids. Aaa provides an N (nitrogen atom) for metal ion complexation;

Bbb is an L- or D-configuration amino acid with an aromatic side chain. Preferred amino acids include D-configuration Phe, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), or Tyr($BzlCl_2$), and derivatives, analogs or homologs thereof. The aromatic ring in Bbb may be functionalized with halogen, alkyl or aryl groups. Bbb provides an N for metal ion complexation;

Ccc is an amino acid that provides both an N, from the alpha amino group, and an S (sulfur atom), from a side chain group, for metal ion complexation. Preferred amino acids include L- or D-configuration Cys, Pen and Hcys;

Lll is a D-configuration amino acid with an aromatic side chain. Preferred amino acids include D-configuration Phe, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), or Tyr($BzlCl_2$), and derivatives, analogs or homologs thereof. The aromatic ring in Lll may be functionalized with halogen, alkyl or aryl groups. Lll does not provide an N for metal ion complexation;

R_2 is an amino acid with an aromatic side chain. Preferred amino acids include L- or D-configuration Phe, Trp, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl) or Tyr($BzlCl_2$), and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids. The C-terminus may be free or amidated. R_2 may also be the corresponding des-carboxyl amino acid of any of the foregoing. Alternatively, R_2 may be eliminated;

Ddd is an amino acid that provides an S, from a side chain group, for metal ion complexation. Preferred amino acids include L- or D-configuration Cys, Pen and Hcys;

R_3 is an amino acid with an aromatic side chain that provides an N for metal ion complexation. Preferred amino acids include L- or D-configuration Phe, Trp, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl) or Tyr($BzlCl_2$), and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids. The C-terminus may be free or amidated. R_3 may also be the corresponding des-carboxyl amino acid of any of the foregoing;

R_4 is a functionality that provides a cationic center. Preferred amino acids include L- or D-configuration Lys, Arg, Orn, Dpr or Dbu, and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids. The N-terminus of the amino acid may be functionalized with any of a variety of neutral amino acid and non-peptide groups, including linear or branched alkyl, aryl, alkene, alkynyl or aralkyl chains;

Eee is an uncharged L- or D-configuration amino acid that provides an N for metal ion complexation. Preferred amino acids include Gly and L-configuration Ala, Nle, Leu, Val, Phe or Trp, and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids. In a preferred embodiment, Eee isn an amino acid with an aliphatic side chain;

Fff is an L- or D-configuration aromatic amino acid. Preferred amino acids include D-configuration Phe, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), Tyr(BzlCl$_2$), Tic, Tiq or Tca, and derivatives, analogs or homologs thereof, including both natural and synthetic amin acids. The aromatic ring in Fff may be substituted with halogen, alkyl or aryl groups. Fff does not provide an N for metal ion complexation;

Ggg is an L- or D-configuration aromatic amino acid. Preferred amino acids include L-configuration Phe, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl) or Tyr(BzlCl$_2$), and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids. The aromatic ring in Ggg may be substituted with halogen, alkyl or aryl groups. Ggg provides an N for metal ion complexation;

R_5 is preferably an amide, substituted amide, ester or carboxylate group. R_5 may also be and L- or D-configuration amino acid or amino acid amide, including an aromatic, aliphatic, neutral or charged amino acid;

Hhh is an L- or D-configuration cationic amino acid with a positively charged side chain. Preferred amino acids include L-configuration Lys, Arg, Orn, Dpr or Dbu, and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids. Hhh does not provide an N for metal ion complexation;

Iii is an L- or D-configuration amino acid that provides an N for metal ion complexation. Preferred amino acids includes Ala, Gly, Nle, Val. Leu, Ile, His, Lys, or Arg, and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids;

Jjj is an L- or D-configuration amino acid with an aromatic side chain. Preferred amino acids include D-configuration Phe, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), or Tyr(BzlCl$_2$), and derivatives, analogs or homologs thereof. The aromatic ring in Jjj may be functionalized with halogens, alkyl or aryl groups. Jjj does not provide an N for metal ion complexation; and

Kkk is an L- or D-configuration cationic amino acid with a positively charged side chain. Preferred amino acids include L-configuration Lys, Arg, Orn, Dpr or Dbu, and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids. Aaa does not provide an N for metal ion complexation.

7. The composition of claim 1 or 2 wherein the metal ion-binding domain is complexed with a m tal ion.

8. The composition of claim 1 or 2, wherein the composition is substantially more specific for one or more melanocortin receptors when the metal ion-binding domain is complexed with a metal ion than is the composition when the metal ion-binding amino acid sequence is not complexed with a metal ion.

9. The combinatorial library of claim 3, 4 or 5 wherein the metal ion-binding domain further comprises at least one N available for binding to a metal ion upon removal of the orthogonal S-protecting group.

10. The combinatorial library of claim 3, 4 or 5 wherein the metal ion-binding domain comprises three residues forming an N_3S_1 ligand.

11. The combinatorial library of claim 3, 4 or 5 wherein the orthogonal S-protecting group is S-thio-butyl, acetamidomethyl, 4-methoxytrityl, S-sulfonate or 3-nitro-2-pyridinesulfenyl.

12. The combinatorial library of claim 3, 4 or 5 wherein the orthogonal S-protecting group may be removed from constituent library members thereof without otherwise altering the constituent library members or any amino acid side chain protecting group therein.

13. The combinatorial library of claim 3, 4 or 5 wherein the structural diversity occurs in the metal ion-binding domain.

14. The combinatorial library of claim 3, 4 or 5 wherein the structural diversity occurs outside the metal ion-binding domain.

15. The combinatorial library of claim 3, 4 or 5 wherein one or more constituent library members include at least one amino acid residue or mimic of an amino acid residue in the sequence at the N- or C-terminus of the metal ion-binding domain containing at least one S wherein the said S is protected by a non-orthogonal S-protecting group, whereby the orthogonal S-protecting group may be removed without removing the non-orthogonal S-protecting group.

16. The solid phase combinatorial library of claim 3 wherein the at least one amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group is an L- or D-3-mercapto amino acid, including but not limited to L- or D-cysteine or L- or D-penicillamine.

17. The combinatorial library of claim 4 or 5 wherein the at least one amino acid residue r mimic of an amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group is an L- or D-3-mercapto amino acid, including but not limited to L- or D-cysteine or L- or D-penicillamine; 3-mercapto phenylananin ; 2-mercaptoacetic acid; 3-mercaptopropionic acid; 2-mercaptopropionic acid; 3-mercapto-3,3,-dim thyl propionic acid; 3-mercapto-3,3,-diethyl proprionic acid; 3-mercapto,3-methyl propionic acid; 2-mercapto,2-methyl acetic acid; 3-cyclop ntamethl n ,3-mercaptopropionic acid; or 2-cyclopentamethlene,2-m rcaptoacetic acid.